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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 17

Complete if Known

Application Number	09/743,920- 10/623 036
Filing Date	November 15, 2000 July 18, 2003
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Woodwine
Attorney Docket Number	018097-032500US-0100.22765

U.S. PATENT DOCUMENTS

Examiner	Cite No. ¹	Document Number Number Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-6,365,408	04-02-2002	Stemmer	
	AB	US-6,361,974	03-26-2002	Short et al.	
	AC	US-6,358,709	03-19-2002	Short et al.	
	AD	US-6,352,842	03-05-2002	Short et al.	
	AE	US-6,323,030	11-27-2001	Stemmer	
	AF	US-6,297,053	10-02-2001	Stemmer	
	AG	US-6,291,242	09-18-2001	Stemmer	
	AH	US-6,287,861	09-11-2002	Stemmer et al.	
	AI	US-6,277,638	08-21-2001	Stemmer	
	AJ	US-6,180,406	01-30-2001	Stemmer	
	AK	US-6,174,673	01-16-2001	Stemmer	
	AL	US-6,171,820	01-09-2001	Short	
	AM	US-6,168,919	01-02-2001	Short	
	AN	US-6,165,793	12-26-2000	Stemmer	
	AO	US-6,132,970	10-17-2000	Stemmer	
	AP	US-6,117,679	09-12-2000	Stemmer	
	AQ	US-6,096,548	08-01-2000	Stemmer	
	AR	US-6,093,873	07-25-2000	Chambon et al.	
	AS	US-6,087,341	07-11-2000	Khavari	
	AT	US-6,087,177	07-11-2000	Wohlstadter	
	AU	US-6,074,853	06-13-2000	Pati et al.	
	AV	US-6,071,889	06-06-2000	Weiss et al.	
	AW	US-6,057,103	05-02-2000	Short	
	AX	US-6,054,267	04-25-2000	Short	
	AY	US-6,051,409	04-18-2000	Hansen et al.	
	AZ	US-6,030,779	02-29-2000	Short	
	BA	US-6,004,788	12-21-1999	Short	
	BB	US-6,001,574	12-14-1999	Short et al.	
	BC	US-5,976,862	11-02-1999	Kauffman et al.	
	BD	US-5,965,415	10-12-1999	Radman	
	BE	US-5,965,408	10-12-1999	Short	
	BF	US-5,958,672	09-28-1999	Short	
	BG	US-5,955,358	09-21-1999	Huse	
	BH	US-5,939,250	08-17-1999	Short	
	BI	US-5,928,905	07-27-1999	Stemmer et al.	
	BJ	US-5,877,402	03-02-1999	Maliga et al.	

Examiner
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Date
Considered

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**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

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Sheet **2** of **17****Complete if Known**

Application Number	09/743,920 10/623 036
Filing Date	November 15, 2000 7/19/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Woodwine
Attorney Docket Number	018097-032500US 0100.22745

U.S. PATENT DOCUMENTS

Examiner	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number Kind Code ² (if known)			
	BK	US-5,871,974	02-16-1999	Huse	
	BL	US-5,866,363	02-02-1999	Piecznik	
	BM	US-5,858,725	01-12-1999	Crowe et al.	
	BN	US-5,851,813	12-22-1998	Desrosiers	
	BO	US-5,843,643	12-01-1998	Ratner	
	BP	US-5,837,458	11-17-1998	Minshull et al.	
	BQ	US-5,834,252	11-10-1998	Stemmer et al.	
	BR	US-5,830,721	11-03-1998	Stemmer et al.	
	BS	US-5,830,696	11-03-1998	Short	
	BT	US-5,824,514	10-20-1998	Kauffman et al.	
	BU	US-5,824,485	10-20-1998	Thompson et al.	
	BV	US-5,824,469	10-20-1998	Horwitz et al.	
	BW	US-5,817,483	10-06-1998	Kauffman et al.	
	BX	US-5,814,476	09-29-1998	Kauffman et al.	
	BY	US-5,811,238	09-22-1998	Stemmer et al.	
	BZ	US-5,808,022	09-15-1998	Huse	
	CA	US-5,795,747	08-18-1998	Henco et al.	
	CB	US-5,783,431	07-21-1998	Peterson et al.	
	CC	US-5,773,267	06-30-1998	Jacobs et al.	
	CD	US-5,770,434	06-23-1998	Huse	
	CE	US-5,763,192	06-09-1998	Kauffman et al.	
	CF	US-5,756,316	05-26-1998	Schellenberger	
	CG	US-5,723,323	03-03-1998	Kauffman et al.	
	CH	US-5,714,316	02-03-1998	Weiner et al.	
	CI	US-5,698,426	12-16-1997	Huse	
	CJ	US-5,679,522	10-21-1997	Modrich	
	CK	US-5,652,116	07-29-1997	Grandi et al.	
	CL	US-5,629,179	05-13-1997	Mierendorf et al.	
	CM	US-5,605,793	02-25-1997	Stemmer	
	CN	US-5,571,708	11-05-1996	Yang et al.	
	CO	US-5,556,772	09-17-1996	Sorge et al.	
	CP	US-5,556,750	06-30-1996	Modrich	
	CQ	US-5,541,309	06-30-1996	Prasher	
	CR	US-5,523,388	06-04-1996	Huse	
	CS	US-5,521,077	05-28-1996	Khosla et al.	
	CT	US-5,514,568	05-07-1996	Stemmer	

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Sheet	3	of	17
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Application Number	09/713,920 10/623,036
Filing Date	November 15, 2000 7/18/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Woolwine
Attorney Docket Number	018097-032500US 0100, 22745

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**INFORMATION DISCLOSURE
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Sheet

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Complete if Known

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Filing Date	November 15, 2000 7/18/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Wodwin
Attorney Docket Number	018097-032500US0100.22765

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁵
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	DW	EP	252 666		12-16-1998			<input type="checkbox"/>
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	FF	WO	94/13804		06-23-1994			<input type="checkbox"/>

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Sheet **5** of **17****Complete if Known**

Application Number	09/743,920 10/623 036
Filing Date	November 15, 2000 7/18/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel C. Woolwine
Attorney Docket Number	018097-032500US 0100.22745

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. ¹	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ²
		Country Code ³	Number ⁴	Kind Code ⁵ (if known)				
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	FH	WO	95/22625		08-24-1995			<input type="checkbox"/>
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	FZ	WO	00/09727		02-24-2000			<input type="checkbox"/>
	GA	WO	00/18906		04-06-2000			<input type="checkbox"/>
	GB	JP	2-303489		12-17-1990			abst. only

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Sheet 6 of 17

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Application Number	09/713,920 10/623,036
Filing Date	November 15, 2000 7/19/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Woolwing
Attorney Docket Number	018097-032500US 0100.227

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	GC	Adey et al., "Preparation of second-generation phage libraries," <i>Phage Disp. Pept. Proteins</i> , eds. Kay et al., pgs. 277-291 (1996).	
	GD	Andersson et al., "Muller's ratchet decreases fitness of a DNA-based microbe", <i>PNAS</i> , 93: 906-907 (January 1996).	
	GE	Arkin et al., "An Algorithm for Protein Engineering: Simulations of Recursive Ensemble Mutagenesis" <i>Proc. Natl. Acad. Sci. USA</i> , 89(16):7811-7815 (1992).	
	GF	Atreya et al., "Construction of in-frame chimeric plant genes by simplified PCR strategies," <i>Plant Mol. Biol.</i> , 19:517-522 (1992).	
	GG	Balint et al., "Antibody Engineering By Parsimonious Mutagenesis", <i>Gene</i> , 137(1):109-118 (1993)	
	GH	Bailey, "Toward a Science of Metabolic Engineering", <i>Science</i> , 252: 1668-1680 (1991).	
	GI	Barrett et al., "Genotypic analysis of multiple loci in somatic cells by whole genome amplification", <i>Nuc. Acids Res.</i> , 23(17): 3488-3492 (1995).	
	GJ	Bartel et al., "Isolation of New Ribozymes From a Large Pool of Random Sequences", <i>Science</i> , 261:1411-1418 (1993)	
	GK	Beaudry et al., "Directed Evolution of an RNA Enzyme," <i>Science</i> , 257:635-641 (1992).	
	GL	Berger et al., "Phoenix Mutagenesis: One-Step Reassembly of Multiply Cleaved Plasmids With Mixtures of Mutant and Wild-Type Fragments," <i>Anal. Biochem.</i> , 214:571-579 (1993).	
	GM	Berkhout et al., "In Vivo Selection of Randomly Mutated Retroviral Genomes," <i>Nucleic Acids Research</i> , 21(22):5020-5024 (1993).	
	GN	Bock et al., "Selection of single-stranded DNA molecules that bind and inhibit human thrombin," <i>Nature</i> , 355:564-566 (February 2, 1992).	
	GO	Cadwell et al., "Randomization of Genes by PCR Mutagenesis," <i>PCR Methods and Applications</i> , 2:28-33 (1992).	
	GP	Calogero et al., "In Vivo Recombination and the Production of Hybrid Genes," <i>Microbiology Letters</i> , 76:41-44 (1992).	

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Considered

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17

Complete if Known

Application Number	097713,920 10/693,036
Filing Date	November 15, 2000- 7/13/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Weidwinge
Attorney Docket Number	048097-032500US-0100-22705

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	GQ	Cameron et al., "Cellular and Metabolic Engineering An Overview", <u>Applied Biochem. Biotech.</u> , 38: 105-140 (1993).	
	GR	Caren et al., "Efficient Sampling of Protein Sequence Space for Multiple Mutants," <u>Biotechnology</u> , 12(5):517-520 (1994).	
	GS	Carter, P., "Improved Oligonucleotide-Directed Mutagenesis Using M13 Vectors," <u>Methods in Enzymology</u> , 154:382-383 (1985).	
	GT	Chakrabarty, "Microbial Degradation of Toxic Chemicals: Evolutionary Insights and Practical Considerations", <u>ASM News</u> , 62(3): 130-137 (1996).	
	GU	Chater, "The Improving Prospects for Yield Increase by Genetic Engineering in Antibiotic-Producing Streptomycetes", <u>Biotechnology</u> , 8: 115-121 (February 1990).	
	GV	Chen et al., "Tuning the activity of an enzyme for unusual environments: Sequential random mutagenesis of subtilisin E for catalysis in dimethylformamide", <u>PNAS</u> , 90: 5618-5622 (June 1993).	
	GW	Clackson et al., "Making antibody fragments using phage display libraries," <u>Nature</u> , 352:624-628 (August 15, 1991).	
	GX	Collet et al., "A Binary plasmid System for shuffling combinatorial antibody Libraries," <u>PNAS</u> , 89(21):10026-10030 (1992).	
	GY	Crameri et al., "Combinatorial Multiple Cassette Mutagenesis Creates All The Permutations Of Mutant And Wild-Type Sequences", <u>Biotechniques</u> , 18(2):194-196 (1995)	
	GZ	Crameri et al., "Improved Green Fluorescent Protein By Molecular Evolution Using DNA Shuffling", <u>Nat. Biotechnol.</u> , 14(3):315-319 (1996)	
	HA	Crameri et al., "Construction And Evolution Of Antibody-Phage Libraries By DNA Shuffling", <u>Nat. Med.</u> , 2(1):100-102 (1996)	
	HB	Crameri et al., "Molecular Evolution Of An Arsenate Detoxification Pathway By DNA Shuffling", <u>Nat. Biotechnol.</u> , 15(5):436-438 (1997)	
	HC	Crameri et al., "DNA Shuffling Of A Family Of Genes From Diverse Species Accelerates Directed Evolution", <u>Nature</u> , 391(3664):288-291 (1998)	
	HD	Crameri et al., "10(20)-Fold aptamer library amplification without gel purification," <u>Nuc. Acids Res.</u> , 21(18):4410 (1993).	

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17

Complete if Known

Application Number	09/743,920 10/623,036
Filing Date	November 15, 2000 7/18/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Wolwin
Attorney Docket Number	018097-032500US 0100.22725

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	HE	Cull et al., "Screening for receptor ligands using large libraries of peptides linked to the C terminus of the <i>lac</i> repressor," <u>PNAS</u> , 89:1865-1869 (March 1992).	
	HF	Cwirla et al., "Peptides on phage: A vast library of peptides for identifying ligands," <u>PNAS</u> , 87:6378-6382 (August 1990).	
	HG	Daugherty et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," <u>Nuc. Acids Res.</u> , 19(9):2471-2476 (1991).	
	HH	Delagrave et al., "Recursive Ensemble Mutagenesis," <u>Protein Engineering</u> , 6(3):327-331 (1993).	
	HI	Delagrave et al., "Searching Sequence Space to Engineer Proteins: Exponential Ensemble Mutagenesis," <u>Biotechnology</u> , 11:1548-1552 (December 1993).	
	HJ	Dieffenbach et al., <u>PCR Primer. A Laboratory Manual</u> , Cold Spring Harbor Laboratory Press, pgs. 583-589, 591-601, 603-612, and 613-621 (1995).	
	HK	Dube et al., "Artificial mutants Generated by the Insertion of Random Oligonucleotides into the Putative Nucleoside Binding Site of the HSV-1 Thymidine Kinase Gene," <u>Biochemistry</u> , 30(51):11760-11767 (1991).	
	HL	Evvin et al., "Substrate-specificity of trypsin investigated by using a genetic selection," <u>PNAS</u> , 87: 6659-6663 (September 1990).	
	HM	Fang et al., "Human Strand-specific Mismatch Repair Occurs by a Bidirectional Mechanism Similar to That of the Bacterial Reaction," <u>J. Biol. Chem.</u> , 268(16): 11838-11844 (June 5, 1993).	
	HN	Feinberg et al., "A Technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity," <u>Anal. Biochem.</u> , 132:6-13 (1983).	
	HO	Fisch et al., "A Strategy Of Exon Shuffling For Making Large Peptide Repertoires Displayed On Filamentous Bacteriophage," <u>Proc Natl Acad Sci USA</u> , 93(15):7761-7766 (1996)	
	HP	Fullen et al., "Genetic Algorithms and Recursive Ensemble Mutagenesis in Protein Engineering," <u>Complexity Int.</u> 1 1994 I, printed from website http://www.csu.edu.au/ci/vol1/fuullen/REM.html on 12/7/99.	
	HQ	Gates et al., "Affinity Selective Isolation Of Ligands From Peptide Libraries Through Display On A Lac Repressor 'Headpiece Dimer'," <u>J. Mol. Biol.</u> , 255(3):373-386 (1996)	
	HR	Ghosh et al., "Arginine-395 Is Required for Efficient in Vivo and in Vitro Aminoacylation of tRNAs by <i>Escherichia coli</i> Methionyl-tRNA Synthetase," <u>Biochemistry</u> , 30:11767-11774 (1991).	

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Complete if Known

Application Number	09/743,920 10/623 036
Filing Date	November 15, 2000 11/15/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Worthing
Attorney Docket Number	018097-032500US-0100 22769

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

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	HS	Goldman et al., "An Algorithmically Optimized Combinatorial Library Screened by digital Imaging Spectroscopy," <u>Biotechnology</u> , 10:1557-1561 (December 1992).	
	HT	Graf et al., "Random circular permutation of genes and expressed polypeptide chains: Application of the method to the catalytic chains of aspartate transcarbamoylase," <u>PNAS</u> , 93:11591-11596 (1996).	
	HU	Gram et al., "In Vitro Selection and Affinity Maturation of Antibodies From a Naïve Combinatorial Immunoglobulin Library", <u>Proc. Natl. Acad. Sci. USA</u> , 89:3576-3580 (1992)	
	HV	Greener et al., "An Efficient Random Mutagenesis Technique Using An E. coli Mutator Strain", <u>Methods in Molecular Biology</u> , 57:375-385 (1995)	
	HW	Harlow et al., "Construction of Linker-Scanning Mutations using the Polymerase Chain Reaction," <u>Methods in Mol. Biol.</u> , 31:87-96 (1994).	
	HX	Heda et al., "A simple <i>in vitro</i> site directed mutagenesis of concatamerized cDNA by inverse polymerase chain reaction," <u>Nuc. Acids Res.</u> , 20(19):5241-5242 (1992).	
	HY	Heim et al., "Wavelength Mutations And Posttranslational Autoxidation Of Green Fluorescent Protein", <u>Proc. Natl. Acad. Sci. USA</u> , 91(26):12501-12504 (1994)	
	HZ	Hermes et al., "Searching Sequence Space by Definably Random Mutagenesis: Improving the Catalytic Potency of an Enzyme," <u>Proc. Natl. Acad. Sci. USA</u> , 87(2):696-700 (1990).	
	IA	Higuchi et al., "A general method of <i>in vitro</i> preparation and specific mutagenesis of DNA fragments: study of protein and DNA interactions," <u>Nuc. Acids Res.</u> , 16(15):7351-7367 (1988).	
	IB	Ho et al., "DNA and Protein Engineering Using the Polymerase Chain Reaction: Splicing by Overlap Extension," <u>DNA and Protein Eng. Techniques</u> , 2(2):50-55 (1990).	
	IC	Ho et al., "Site-Directed Mutagenesis by Overlap Extension Using the Polymerase Chain Reaction," <u>Gene</u> , 77:51-59 (1989).	
	ID	Hodgson, "The Whys and Wherefores of DNA Amplification," <u>Biotechnology</u> , 11:940-942 (August 1993).	
	IE	Horton et al., "Gene Splicing by Overlap Extension," <u>Methods in Enzymology</u> , 217:270-279 (1993).	
	IF	Horton et al., "Gene Splicing by Overlap Extension: Tailor-Made Genes Using the Polymerase chain Reaction," <u>BioTechniques</u> , 8(5):528-535 (May 1990).	

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Sheet 10 of 17

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Application Number	09/743,920 10/623 036
Filing Date	November 15, 2000 7/18/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Woodwine
Attorney Docket Number	018097-032500US0100.22765

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	IG	Horton et al., "Engineering Hybrid Genes Without the Use of Restriction Enzymes: Gene Splicing by Overlap Extension," <u>Gene</u> , 77:61-68 (1989).	
	IH	Ippolito et al., "Structure assisted redesign of a protein-zinc-binding site with femtomolar affinity," <u>PNAS</u> , 92: 5017-5021 (May 1995).	
	II	Janczewski et al., "Molecular phylogenetic inference from saber-toothed cat fossils of Rancho La Brea," <u>PNAS</u> , 89:9769-9773 (1992).	
	IJ	Jayaraman et al., "Polymerase chain reaction-mediated gene synthesis: Synthesis of a gene coding for isozyme c of horseradish peroxidase," <u>PNAS</u> , 88:4084-4088 (May 1991).	
	IK	Jones et al., "A Rapid Method for Recombination and Site-Specific Mutagenesis by Placing Homologous ends on DNA Using Polymerase Chain Reaction," <u>BioTechniques</u> , 10(1): 62-66 (1991).	
	IL	Jones et al., "Recombinant Circle PCR and Recombination PCR for Site-Specific Mutagenesis Without PCR Product Purification," <u>Biotechniques</u> 12(4):528-534 (1992).	
	IM	Joyce, G. F., "Directed Molecular Evolution," <u>Scientific American</u> , (December 1992).	
	IN	Kang et al., "Antibody redesign by chain shuffling from random combinatorial immunoglobulin libraries," <u>PNAS</u> , 88(24):11120-11123 (1991).	
	IO	Kellogg et al., "Plasmid-Assisted Molecular Breeding: New Technique for Enhanced Biodegradation of Persistent Toxic Chemicals," <u>Science</u> , 214: 1133-1135 (December 4, 1981).	
	IP	Kim et al., "Cloning and Nucleotide Sequence of the Colb Shufflon," <u>Plasmid</u> , 22:180-184 (1989).	
	IQ	Kim et al., "Human Immunodeficiency Virus Reverse Transcriptase," <u>The Journal of Biological Chemistry</u> , 271(9):4872-4878 (1996).	
	IR	Klug et al., "Creating chimeric molecules by PCR directed homologous DNA recombination," <u>Nuc. Acids Res.</u> , 19(10):2793 (1991).	
	IS	Komano et al., "Physical and Genetic Analyses of IncI2 Plasmid R721: Evidence for the Presence of Shufflon," <u>Plasmid</u> , 23:248-251 (1990).	
	IT	Komano et al., "Distribution of Shufflon among IncI Plasmids," <u>J. Bacteriology</u> , 169(11):5317-5319 (1987).	

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**INFORMATION DISCLOSURE
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Sheet

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17

Complete if Known

Application Number	09/743,920 10/633 036
Filing Date	November 15, 2000 7/19/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Wadiwire
Attorney Docket Number	018697-032500US-0100.23748

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

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	IU	Kramer et al., "Oligonucleotide-directed construction of mutations via gapped duplex DNA," <u>Methods in Enzymology</u> , 154:350-367 (1987).	
	IV	Krishnan et al., "Direct and crossover PCR amplification to facilitate Tn5supF-based sequencing of λ phage clones," <u>Nuc. Acids Res.</u> , 19(22):6177-6182 (1991).	
	IW	Kunkel et al., "Rapid and efficient site-specific mutagenesis without phenotypic selection," <u>Methods in Enzymology</u> , 154:367-382 (1987).	
	IX	Kunkel, "Rapid and efficient site-specific mutagenesis without phenotypic selection", <u>PNAS</u> , 82: 488-493 (January 1985).	
	IY	Leung et al., "A Method For Random Mutagenesis of a Defined DNA Segment Using a Modified Polymerase Chain Reaction," <u>Techniques</u> , 1:11-15 (1989).	
	IZ	Levichkin et al., "A New Approach to Construction of Hybrid Genes: Homolog Recombination Method", <u>Mol. Biology</u> , 29(5) part 1: 572-577 (1995).	
	JA	Lewis et al., "Efficient site directed <i>in vitro</i> mutagenesis using ampicillin selection", <u>Nuc. Acids Res.</u> , 18(12): 3439-3443 (1990).	
	JB	Lorberboum-Calski et al., "Cytotoxic activity of an interleukin 2- <i>Pseudomonas</i> exotoxin chimeric protein produced in <i>Escherichia coli</i> ," <u>PNAS</u> , 85:1922-1926 (1988).	
	JC	Lowman, H.B. et al, "Affinity Maturation of Human Growth Hormone by Monovalent Phage Display," <u>J. Mol. Biol.</u> , 234:564-578 (1993).	
	JD	Majumder, K., "Ligation-free gene synthesis by PCR: synthesis and mutagenesis at multiple loci of a chimeric gene encoding OmpA signal peptide and hirudin," <u>Gene</u> , 110:89-94 (1992).	
	JE	Marks et al., "By-passing Immunization, Human Antibodies from V-gene Libraries Displayed on Phage," <u>J. Mol. Biol.</u> , 222:581-597 (1991).	
	JF	Marks et al., "By-Passing Immunization: Building High Affinity Human Antibodies by Chain Shuffling," <u>Bio/Technology</u> , 10:779-783 (1992).	
	JG	Marton et al., "DNA Nicking Favors PCR Recombination", <u>Nucleic Acids Res.</u> , 19(9):2423-2426 (1991)	
	JH	Maryon et al., "Characterization of recombination intermediates from DNA injected into <i>Xenopus laevis</i> oocytes: evidence for a nonconservative mechanism of homologous recombination," <u>Mol. Cell Biol.</u> , 11(6):3278-3287 (1991).	

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Sheet 12 of 17**Complete if Known**

Application Number	09/743,920 10/623,036
Filing Date	November 15, 2000 7/18/03
First Named Inventor	Stemmer
Art Unit	1048 1637
Examiner Name	Park, H. Samuel Workwine
Attorney Docket Number	048097-032500US 0100.22745

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

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	J1	McCafferty et al., "Phage antibodies: filamentous phage displaying antibody variable domains," <u>Nature</u> , 348:552-554 (December 6, 1990).	
	JJ	Meyerhans et al., "DNA Recombination During PCR," <u>Nucleic Acids Research</u> , 18(7):1687-1691 (1990).	
	JK	Michael, S.F., "Thermostable Ligase-Mediated Incorporation of Mutagenic Oligonucleotides During PCR Amplification," chapter 19 from <i>Methods in Molecular Biology, PCR Cloning Protocols from Molecular Cloning to Genetic Engineering</i> , eds. B. White, Humana Press, totowa, New Jersey, pages 189-195 (1997).	
	JL	Moore et al., "Directed evolution of a <i>para</i> -nitrobenzyl esterase for aqueous-organic solvents", <u>Nature Biotech.</u> , 14: 458-467 (April 1996).	
	JM	Mori et al., "Group II intron RNA-catalyzed recombination of RNA <i>in vitro</i> ," <u>Nuc. Acids Res.</u> , 18(22):6545-6551 (1990).	
	JN	Mullis et al., "Specific Synthesis of DNA <i>in Vitro</i> via a Polymerase-Catalyzed Chain Reaction," <u>Methods in Enzymology</u> , 155:335-351 (1987).	
	JO	Mullis et al., "Specific Enzymatic Amplification of DNA In Vitro: The Polymerase Chain Reaction," Cold Spring Harbor Symposia on Quantitative Biology, 51:263-273 (1986).	
	JP	Near, "Gene Conversion Of Immunoglobulin Variable Regions In Mutagenesis Cassettes By Replacement PCR Mutagenesis", <u>Biotechniques</u> , 12(1):88-97 (1992)	
	JQ	Ner et al., "LABORATORY METHODS: A Simple and Efficient Procedure for Generating Random Point Mutations and for Codon Replacements Using Mixed Oligodeoxynucleotides," <u>DNA</u> , 7(2):127-134 (1988).	
	JR	Nissim et al., "Antibody fragments from a 'single pot' display library as immunochemical reagents," <u>EMBO Journal</u> , 13(3):692-698 (1994).	
	JS	Oliphant et al., "Cloning of Random-Sequence Oligodeoxynucleotides," <u>Gene</u> , 44(2-3):177-183 (1986).	
	JT	Olsen et al., "Hybrid Bacillus (1-3,1-4)-beta-glucanases: engineering thermostable enzymes by construction of hybrid genes," <u>Mol. Gen. Genet.</u> , 225(2):177-185 (1991).	
	JU	Omura, "Philosophy of New Drug Discovery", <u>Microbiol. Rev.</u> , 50(3): 259-279 (September 1986).	
	JV	Osuna et al., "Combinatorial mutagenesis of three major groove-contacting residues of <i>Eco</i> RI: single and double amino acid replacements retaining methyltransferase-sensitive activities," <u>Gene</u> , 106:7-12 (1991).	

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Sheet

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of

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Complete if Known

Application Number

097743,920 10/623 036

Filing Date

November 15, 2000 7/19/03

First Named Inventor

Stemmer

Art Unit

1648 1637

Examiner Name

Park, H. Samuel Woodwine

Attorney Docket Number

018097-032500US 0100.23 TUS

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	JW	Paabo et al., "DNA Damage Promotes Jumping between Templates during Enzymatic Amplification," <u>J. Biol. Chem.</u> , 265(8):4718-4721 (March 15, 1990).	
	JX	Perlak, "Single Step Large Scale Site-Directed In Vitro Mutagenesis Using Multiple Oligonucleotides", <u>Nucleic Acids Res.</u> , 18(24):7457-7458 (1990)	
	JY	<u>Pharmacia Catalog</u> , pp. 70-71 (1993 Edition).	
	JZ	Piepersberg, "Pathway Engineering in Secondary Metabolite-Producing Actinomycetes", <u>Crit. Rev. Biotech.</u> , 14(3):251-285 (1994).	
	KA	Pompon et al., "Protein Engineering by cDNA Recombination in Yeasts: Shuffling of Mammalian Cytochrome P-450 Functions," <u>Gene</u> , 83(1):15-24 (1989).	
	KB	Prasher, "Using GFP to see the light", <u>TIG</u> , 11(8) (August 1995).	
	KC	Prodromou et al., "PROTOCOL, Recursive PCR: a novel technique for total gene synthesis," <u>Protein Engineering</u> , 5(8):827-829 (1992).	
	KD	Rao et al., "Recombination and Polymerase Error Facilitate Restoration of Infectivity in Brome Mosaic Virus," <u>Journal of Virology</u> , 67(2):969-979 (1993).	
	KE	Rapley, "Enhancing PCR Amplification And Sequencing Using DNA-Binding Proteins", <u>Mol. Biotechnol.</u> , 2(3):295-298 (1994)	
	KF	Reidhaar-Olson et al., "Combinatorial Cassette Mutagenesis as a Probe of the Informational Content of Protein Sequences," <u>Science</u> , 241:53-57 (1988).	
	KG	Rice et al., "Random PCR mutagenesis screening of secreted proteins by direct expression in mammalian cells", <u>PNAS</u> , 89: 5467-5471 (June 1992).	
	KH	Robles et al., "Hydropathy and Molar Volume Constraints on Combinatorial mutants of the Photosynthetic Reaction Center," <u>J. Mol. Biol.</u> , 232:242-252 (1993).	
	KI	Rouwendal et al., "Simultaneous Mutagenesis of Multiple Sites: Application of the Ligase Chain Reaction Using PCR Products Instead of Oligonucleotides," <u>BoiTechniques</u> , 15(1):68-70, 72-74, 76 (1993).	
	KJ	Saiki et al., "Diagnosis of sickle Cell Anemia and β -Thalassemia with Enzymatically Amplified DNA and Nonradioactive Allele-Specific Oligonucleotide Probes," <u>New England J. of Medicine</u> , 319(9):537-541 (September 1, 1988).	

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Sheet **14** of **17****Complete if Known**

Application Number	09/743,920 10/623,036
Filing Date	November 15, 2000- 7/18/03
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Walwino
Attorney Docket Number	048097-032500US010022765

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	KK	Saiki et al., "analysis of enzymatically amplified β -globin and HLA-DQ α DNA with allele-specific oligonucleotide probes," <u>Nature</u> , 324:163-166 (November 13, 1986).	
	KL	Saiki et al., "Enzymatic Amplification of β -Globin Genomic Sequences and Restriction Site analysis for Diagnosis of Sickle Cell Anemia," <u>Science</u> , 230:1350-1354 (December 20, 1985).	
	KM	Saiki et al., "Primer-Directed Enzymatic Amplification of DNA with a Thermostable DNA Polymerase," <u>Science</u> , 239:487-491 (January 20, 1988).	
	KN	Sambrook et al., <u>Molecular Cloning, A Laboratory Manual</u> , Cold Spring Laboratory Press, Cold Spring Harbor, New York (1989).	
	KO	Sambrook et al., <u>Molecular Cloning: A Laboratory Manual</u> , 2nd edition, Cold Spring Harbor Laboratory Press, pages 14.2, 14.34, and 14.35 (1989).	
	KP	Sandhu et al., "Dual Asymmetric PCR: One-Step Construction of Synthetic Genes," <u>BioTechniques</u> , 12(1):14-16 (1992).	
	KQ	Scharf et al., "Direct Cloning and Sequence Analysis of Enzymatically Amplified Genomic Sequences," <u>Science</u> , 233:1076-1078 (September 1986).	
	KR	Scott et al., "Searching for Peptide Ligands with an Epitope Library," <u>Science</u> , 249:386-390 (July 20, 1990).	
	KS	Shao et al., "Random-priming <i>in vitro</i> recombination: an effective tool for directed evolution," <u>Nuc. Acids Res.</u> , 26(2):681-683 (1998).	
	KT	Shi et al., "Rapid PCR Construction of a Gene Containing Lym-1 Antibody Variable Regions," <u>PCR Methods and Applications</u> , 3:46-53 (1993).	
	KU	Shuldiner et al., "Hybrid DNA artifact from PCR of closely related target sequences," <u>Nuc. Acids Res.</u> , 17(11):4409 (1989).	
	KV	Sikorski et al., "In Vitro Mutagenesis and Planned Shuffling: From Cloned Gene to Mutant Yeast," <u>Methods in Enzymology</u> , 194:302-318 (1991).	
	KW	Simpson et al., "Two paradigms of metabolic engineering applied to amino acid biosynthesis," <u>Biochem. Soc. Transactions</u> , vol. 23 (1995).	
	KX	Smith et al., "Unwanted Mutations in PCR Mutagenesis: Avoiding the Predictable," <u>PCR Methods and Applications</u> , 2(3):253-257 (February 1993).	

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of

17

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Application Number	09/743,920 10/623 036
Filing Date	November 15, 2000 11/15/00
First Named Inventor	Stemmer
Art Unit	1648 1637
Examiner Name	Park, H. Samuel Woodwine
Attorney Docket Number	048097-032500US-0100.227US

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	KY	Smith et al., "Localized sex in bacteria," <u>Nature</u> , 349:29-31 (1991).	
	KZ	Steele et al., "Techniques for Selection of Industrially Important Microorganisms", <u>Ann. Rev. Microbiol.</u> , 45: 89-106 (1991).	
	LA	Stemmer, "Rapid Evolution of a Protein in Vitro by DNA Shuffling," <u>Nature</u> , 370:389-391 (1994).	
	LB	Stemmer, "DNA Shuffling by Random Fragmentation and Reassembly: In Vitro Recombination for Molecular Evolution" <u>Proc. Natl. Acad. Sci. USA</u> , 91(22):10747-10751 (1994).	
	LC	Stemmer et al., "Selection of an Active Single Chain FV Antibody from a Protein Linker Library Prepared by Enzymatic Inverse PCR," <u>Biotechniques</u> , 14(2):256-265 (1992).	
	LD	Stemmer, "Searching Sequence Space", <u>Biotechnology</u> , 13:549-553 (1995)	
	LE	Stemmer et al., "Single-Step Assembly Of A Gene And Entire Plasmid From Large Numbers Of Oligodeoxyribonucleotides", <u>Gene</u> , 164(1):49-53 (1995)	
	LF	Stemmer, "The Evolution of Molecular Computation", <u>Science</u> , 270(5241):1510 (1995)	
	LG	Stemmer, "Sexual PCR and Assembly PCR" <u>Encyclopedia Mol. Biol.</u> , VCH Publishers, New York, pp. 447-457 (1996)	
	LH	Stemmer et al., "Increased Antibody Expression from Escherichia-Coli Through Wobble-Base Library Mutagenesis by Enzymatic Inverse PCR," <u>Gene</u> , 123(1):1-7 (1993).	
	LI	Stemmer et al., "Enzymatic Inverse PCR - A Restriction Site Independent, single-Fragment Method for High-Efficiency, Site-Directed Mutagenesis," <u>Biotechniques</u> , 13(2):214 (1992).	
	LJ	Stemmer et al., "Expression of Antibody FV Fragments Specific for a Heavy Metal Chelate Indium Edta In Escherichia-Coli," <u>J. Cell Biochem., Suppl.</u> 0(15 part G), pg. 217 (1991).	
	LK	Stemmer et al., "A 20-Minute Ethidium Bromide High-slat Extraction Protocol for Plasmid DNA," <u>Biotechniques</u> , 10(6):726 (1991).	
	LL	Stephanopoulos et al., "Metabolic engineering - methodologies and future prospects", <u>Trends Biotech.</u> 11: 392-396 (1993).	

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First Named Inventor	Stemmer
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Examiner Name	Park, H. Samuel Worlwin
Attorney Docket Number	048097-032500US 0100.227US

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	LM	Stephanopoulos, "Metabolic engineering", <u>Curr. Opin. Biotech.</u> , 5: 196-200 (1994).	
	LN	Villarreal et al., "A General Method of Polymerase-Chain-Reaction-Enabled Protein Domain Mutagenesis: Construction of a Human Protein S-Osteonectin Gene," <u>Analytical Biochem.</u> , 197:362-367 (1991).	
	LO	Wang et al., "Identification Of Glial Filament Protein And Vimentin In The Same Intermediate Filament System In Human Glioma Cells", <u>Proc. Natl. Acad. Sci. USA</u> , 81(7):2102-2106 (1984)	
	LP	Weber et al., "Formation of Genes Coding for Hybrid Proteins by Recombination Between Related, Cloned Genes in E. Coli," <u>Nucleic Acids Research</u> , 11(16):5661-5669 (1983)	
	LQ	Wehmeier, "New multifunctional <i>Escherichia coli-Streptomyces</i> shuttle vectors allowing blue-white screening on XGal plates", <u>Gene</u> , 165: 149-150 (1995).	
	LR	Weissenhorn et al., "Chimerization of antibodies by isolation of rearranged genomic variable regions by the polymerase chain reaction," <u>Gene</u> , 106:273-277 (1991).	
	LS	Winter et al., "Making Antibodies By Phage Display Technology", <u>Ann. Rev. Immunol.</u> , 12:433-455 (1994)	
	LT	Wu et al., "Allele-specific enzymatic amplification of beta-globin genomic for diagnosis of sickle cell anemia," <u>PNAS</u> , 86(6):2757-2760 (1989).	
	LU	Yao et al., "Site-directed Mutagenesis of Herpesvirus Glycoprotein Phosphorylation Sites by Recombination Polymerase Chain Reaction," <u>PCR Methods and Applications</u> , 1(3):205-207 (February 1992).	
	LV	Yolov et al., "Constructing DNA by polymerase recombination," <u>Nuc. Acids Res.</u> , 18(13):3983-3986 (1990).	
	LW	Yon et al., "Precise gene fusion by PCR," <u>Nuc. Acids Res.</u> , 17(12):4895 (1989).	
	LX	Youvan et al., "Recursive Ensemble Mutagenesis: A Combinatorial Optimization Technique for Protein Engineering," from <u>Parallel Problem Solving from Nature</u> , 2, Manner eds., pp. 401-410 (1992).	
	LY	Zhang et al., "Directed Evolution Of A Fucosidase From A Galactosidase By DNA Shuffling And Screening", <u>Proc. Natl. Acad. Sci. USA</u> , 94(9):4504-4509 (1997)	
	LZ	Zhao et al., "Molecular Evolution by Staggered Extension Process (StEP) In Vitro Recombination", <u>Nature Biotech.</u> , 16:258-261 (1998)	

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Art Unit	1648 1637
Examiner Name	Park, H. Samuel W. W. W. W.
Attorney Docket Number	048097-032500US-010022745

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	MA	Zoller et al., "Oligonucleotide-directed mutagenesis: a simple method using two oligonucleotide primers and a single-stranded DNA template," <i>Methods in Enzymology</i> , 154:329-350 (1987).	
	MB	Zoller, M.J., "New recombinant DNA methodology for protein engineering," <i>Curr. Opin. Biotech.</i> , 3:348-354 (1992).	
	MC	Biotransformations, Pathogenesis, and Evolving Biotechnology, Program and Abstracts, Pseudomonas '89, American Society for Microbiology and The University of Illinois, 7/9-13/89, abstracts 11-21 to 11-25.	
	MD	Statutory Declaration of Mae Li Gan in Australian Opposition against application 703264.	
	ME	Statutory Declaration of Dr. Gerald Joyce in Australian Opposition against application 703264.	
	MF	Statutory Declaration of Ngarie Petit-Young in Australian Opposition against application 703264.	
	MG	Statutory Declaration of Ruth Bird in Australian Opposition against application 703264.	
	MH	Request for leave to amend the Statement of Grounds and Particulars re: opposition 703264 in Australia (1/25/01).	
	MI	Amended Statement of Particulars re: opposition 703264 in Australia (1/25/01).	
	MJ	Opposition Statement in matter of Australian Patent Application 703264 (Affymax Technologies NV), filed by Diversa Corporation on September 23, 1999.	

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